SUPPLEMENTARY DATA

The Effect of Alcohol Consumption on Insulin Sensitivity and Glycemic Status
A systematic review and meta-analysis of intervention studies

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Short title: Alcohol Consumption and Insulin Sensitivity

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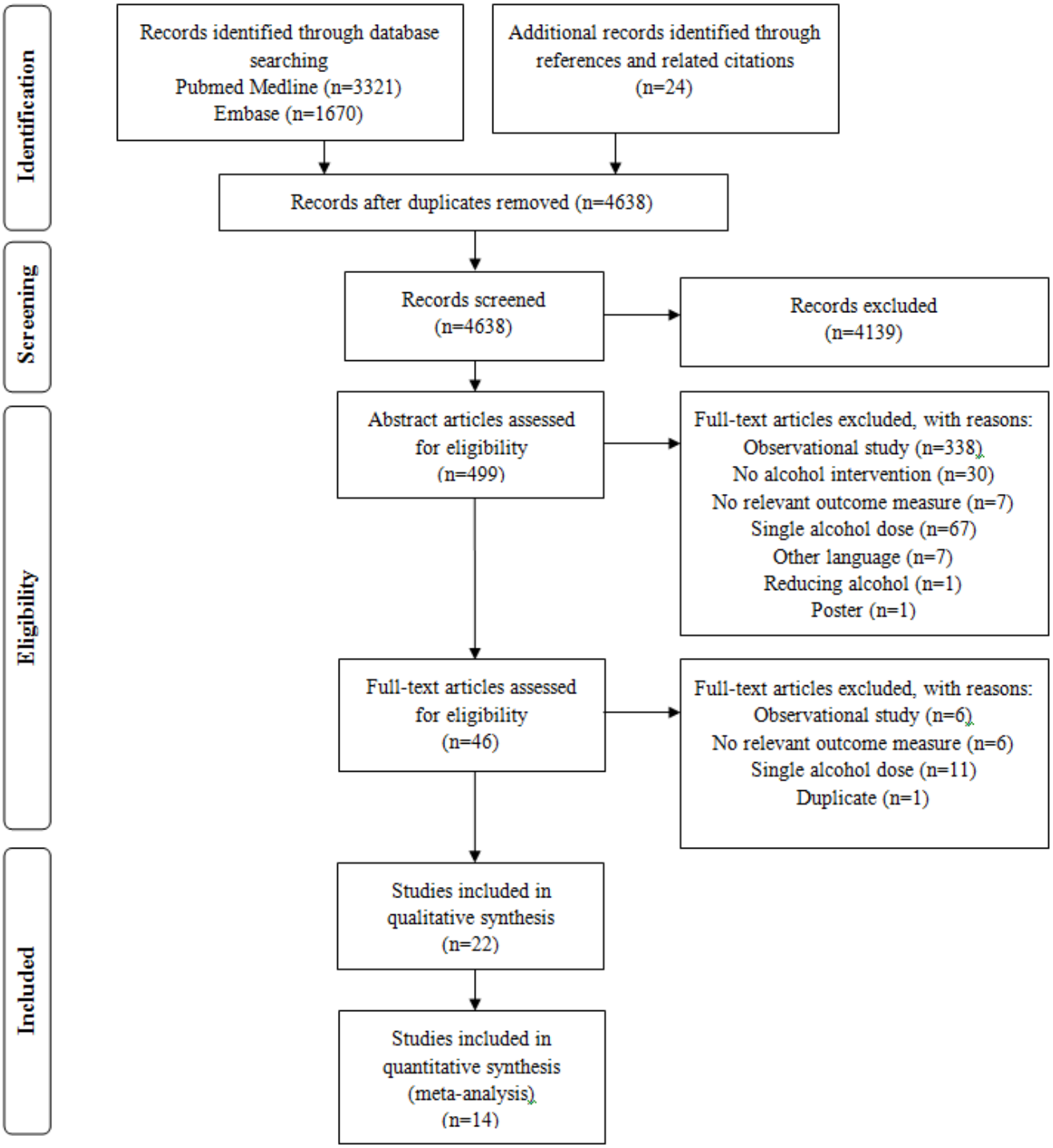
Supplementary Text 1. Pre-specified search string

Pubmed Medline
"((alcohol [Title/Abstract] OR ethanol [Title/Abstract])
AND
(intake [Title/Abstract] OR consumption [Title/Abstract])) OR (alcoholic [Title/Abstract] AND (beverage [Title/Abstract] OR beverages [Title/Abstract] OR drink [Title/Abstract] OR drinks [Title/Abstract]))
AND
(Insulin [Title/Abstract] OR glycemic control [Title/Abstract] OR glycaemic control [Title/Abstract] OR glycemic response [Title/Abstract] OR glycaemic response [Title/Abstract] OR glucose [Title/Abstract] OR HbA1c [Title/Abstract] OR Hb A1c [Title/Abstract] OR HbA1 [Title/Abstract] OR HB A1 [Title/Abstract] OR Glycemic [Title/Abstract] OR Glycemia [Title/Abstract] OR Hemoglobin [Title/Abstract] OR Haemoglobin [Title/Abstract])
NOT (Animals [Mesh] NOT Humans [Mesh]))"

Embase
alcohol:ti:ab OR ethanol:ti:ab
AND
intake:ti:ab OR consumption:ti:ab OR alcoholic:ti:ab AND beverage:ti:ab OR beverages:ti:ab OR drink:ti:ab OR drinks:ti:ab
AND
Insulin:ti:ab OR 'glycemic control':ti:ab OR 'glycaemic control':ti:ab OR 'glycemic response':ti:ab OR 'glycaemic response':ti:ab OR glucose:ti:ab OR HbA1c:ti:ab OR 'Hb A1c':ti:ab OR HbA1:ti:ab OR 'HB A1':ti:ab OR Glycemic:ti:ab OR Glycemia:ti:ab OR Hemoglobin:ti:ab OR Haemoglobin:ti:ab
AND
[embase]/lim NOT [medline]/lim NOT ([animals]/lim NOT [humans]/lim)

SUPPLEMENTARY DATA

Supplementary Figure 1. Flow chart of the multi-phase process for study selection.



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Supplementary Table 1. Quality assessment of selected studies (n=22)

Study	Design	Randomized	Randomization procedure	Control group	Blinding	Drop out rates*	Measurement compliance	Intention to treat analysis	Funding	Jadad score (0-5)†	Included in meta-analysis‡
Bantle et al. (2008)	Crossover	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	2	No[§]
Beulens et al. (2006)	Crossover	Yes	NR	Yes	NR	Yes	Yes	No	Yes	2	Yes
Beulens et al. (2007)	Crossover	Yes	NR	Yes	NR	Yes	Yes	Yes	Yes	2	Yes
Beulens et al. (2008)	Crossover	Yes	Yes	Yes	NR	Yes	Yes	Yes	Yes	3	Yes
Bhathena et al. (1995)	Crossover	Yes	Yes	Yes	NR	NR	NR	NR	NR	2	Yes
Cesena et al. (2011)	Parallel	No	NA	Yes	NR	Yes	Yes	Yes	Yes	1	No[‖]
Chiva-Blanch et al. (2013)	Crossover	Yes	Yes	Yes	No	Yes	Yes	No	Yes	3	Yes
Contaldo et al. (1989)	Crossover	Yes	NR	Yes	NR	NR	NR	NR	Yes	1	Yes
Cordain et al. (1997)	Crossover	No	NA	Yes	NR	Yes	Yes	Yes	Yes	1	No[‖]
Cordain et al. (2000)	Crossover	Yes	NR	Yes	NR	Yes	Yes	Yes	NR	2	Yes
Davies et al. (2002)	Crossover	Yes	NR	Yes	NR	Yes	NR	No	NR	2	Yes
Flechtner-Mors et al. (2004)	Parallel	Yes	NR	Yes	NR	Yes	Yes	No	Yes	2	Yes
Joosten et al. (2008)	Crossover	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	3	Yes
Joosten et al. (2011) [¶]	Crossover	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	3	Yes
Joosten et al. (2012) [¶]	Crossover	Yes	Yes	Yes	No	Yes	Yes	Yes	Yes	3	Yes
Kim et al. (2009)	Parallel	No	NA	Yes	NR	Yes	Yes	No	Yes	1	No[‖]
Lavy et al. (1994)	Parallel	Yes	NR	No	NR	NR	NR	NR	NR	1	No[#]
Queipo-Ortuno et al. (2012)	Crossover	Yes	NR	Yes	NR	Yes	Yes	Yes	No	2	Yes
Romeo et al. (2008)	Parallel	No	NA	Yes	NR	Yes	Yes	No	Yes	1	No[‖]
Shai et al. (2007)	Parallel	Yes	NR	Yes	NR	Yes	Yes	No	Yes	2	No[§]
Sierksma et al. (2004)	Crossover	Yes	NR	Yes	No	Yes	Yes	No	Yes	2	Yes
Zheng et al. (2012)	Parallel	Yes	NR	No	NR	Yes	Yes	No	Yes	2	No[#]

* The studies that reported drop outs also reported the reasons for withdrawal.
† Jadad score is based on description of randomization and randomization procedure, blinding and blinding procedure, and dropout rates and reasons for withdrawal.
¶ Results of the studies of Joosten et al. (2011 and 2012) are partly published in Joosten et al. (2014).
‡ Reason for exclusion from meta-analysis: § Participants with type 2 diabetes; ‖No randomized design; #No control group.
NR: Not reported; NA: Not applicable

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Supplementary Table 2. Publication bias calculated by Egger's and Begg's test.

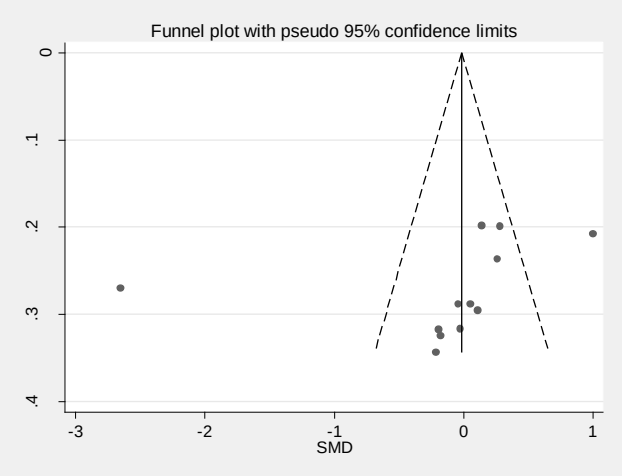
	Egger's test	**Begg's test**	**Begg test (continuity corrected)**
ISI	0.01*	0.02*	0.04*
HOMA-IR	0.29	0.33	0.46
ISI & HOMA-IR	0.26	0.02*	0.02*
- Women	0.13	0.33	0.46
- Men	0.47	0.29	0.37
Insulin	0.18	0.30	0.35
- Women	0.17	0.85	1.00
- Men	NA	NA	NA
Glucose	0.01*	0.01*	0.01*
- Women	0.03*	0.05	0.09
- Men	0.05*	0.04	0.09
HbA_{1c}	0.28	0.12	0.30

* $p<0.05$ indicates evidence for publication bias.

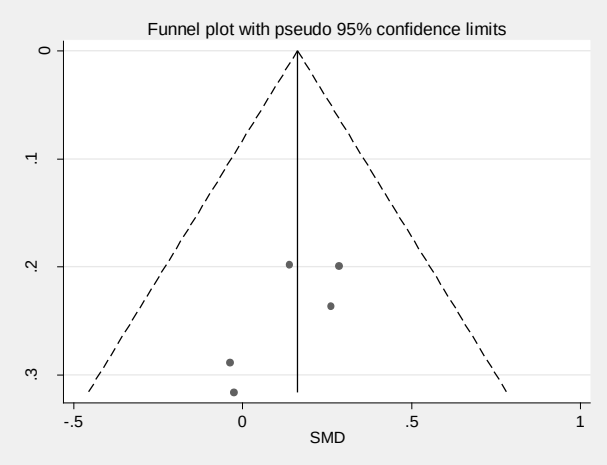
SUPPLEMENTARY DATA

Supplementary Figure 2. Funnel plots of all endpoints for identification of publication bias

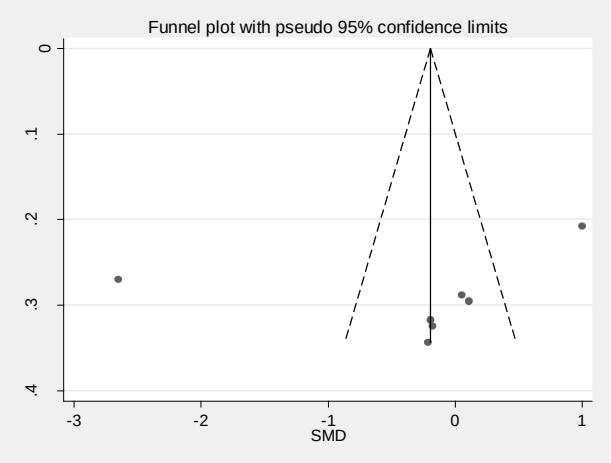
ISI & HOMA-IR (all)



ISI & HOMA-IR (women)

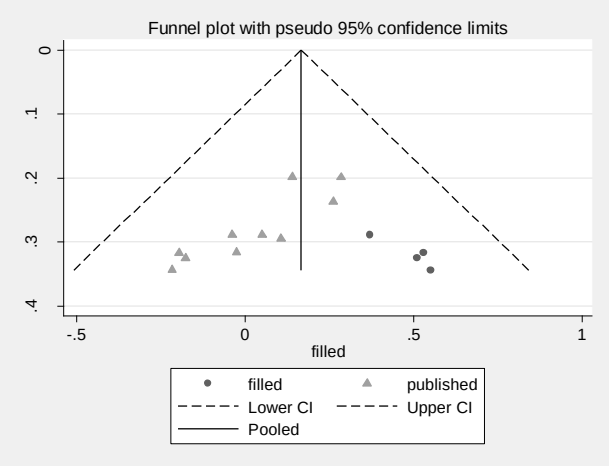


ISI & HOMA-IR (men)



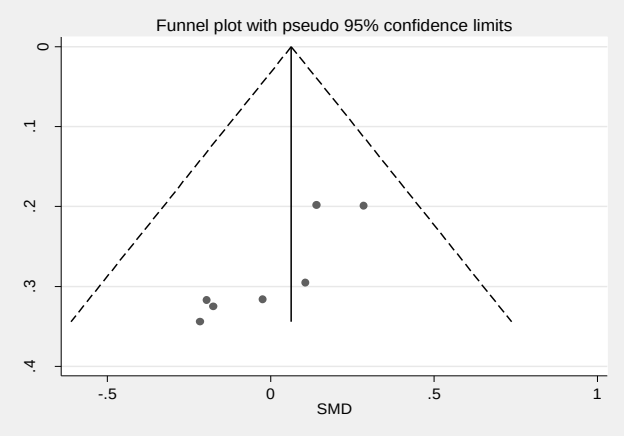
SUPPLEMENTARY DATA

ISI & HOMA-IR (using the trim and fill method by Duval and Tweedie to adjust for publication bias)*

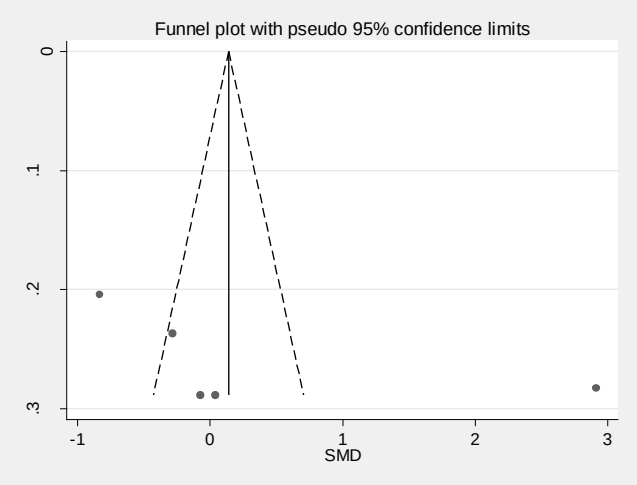


* The data from the study arms of Chiva-Blanch et al. (2013) were excluded, as they induced heterogeneity.

ISI (all)

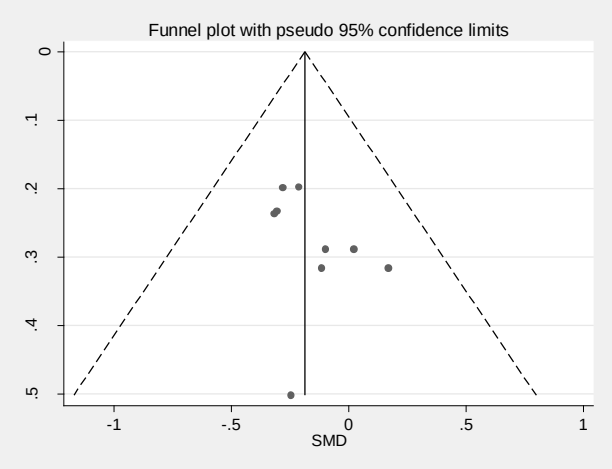


HOMA-IR (all)

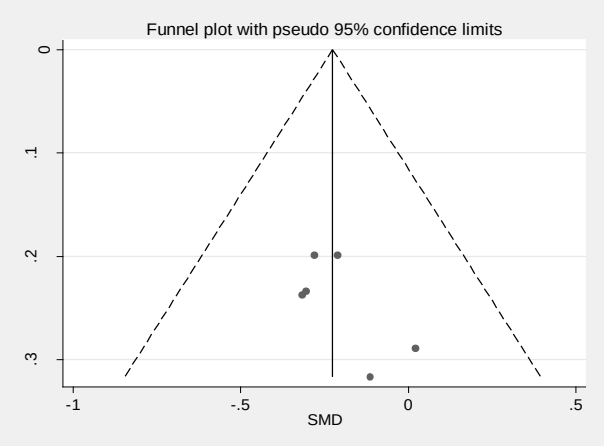


SUPPLEMENTARY DATA

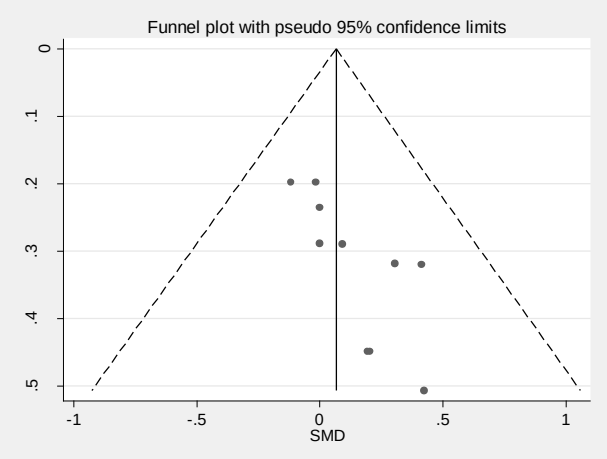
Insulin (all)



Insulin (women)

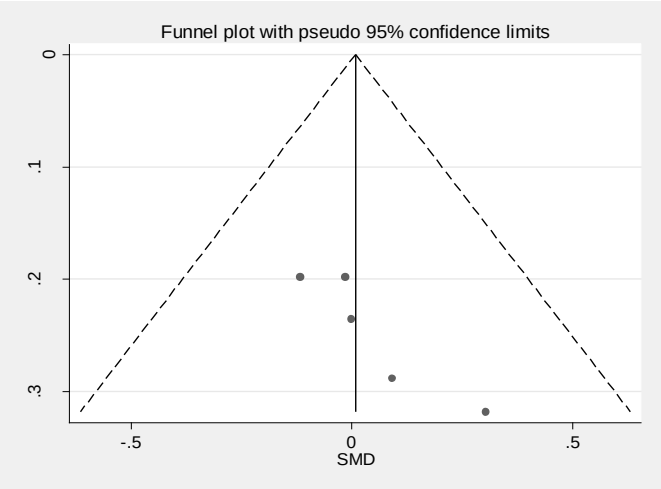


Glucose (all)

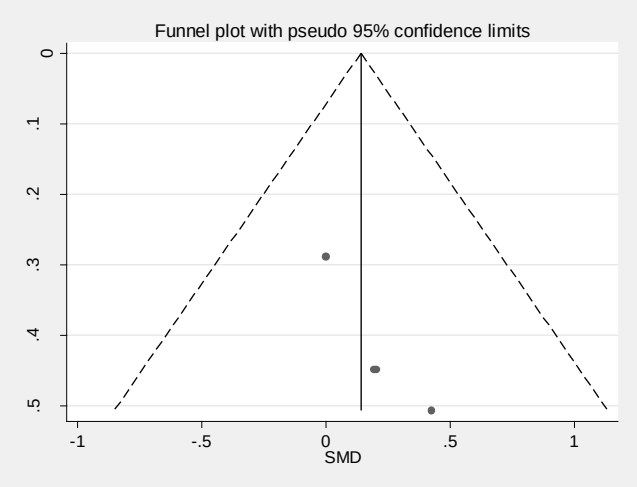


SUPPLEMENTARY DATA

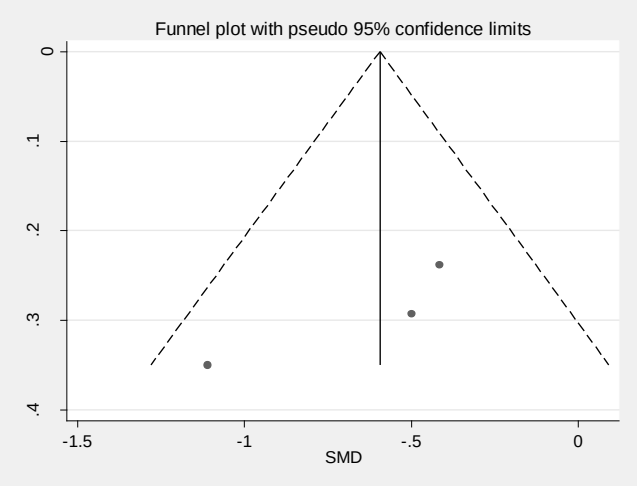
Glucose (women)



Glucose (men)



HbA$_{1c}$ (all)



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PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	3
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	4
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Suppl. Text 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	4-5, Suppl. Fig. 1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5

Section/topic	#	Checklist item	Reported on page #
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-6
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	6
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	6-7
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	7, Suppl. Fig.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	7-8, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8, Suppl. Table 2
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Fig. 1,2,3
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-10
Section/topic	**#**	**Checklist item**	**Reported on page #**
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10-11, Suppl. Fig. 2
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-10

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DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11-13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	13-14
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	15-16
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	17

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

SUPPLEMENTARY DATA

JULIUS CENTER UMC UTRECHT

Protocol

The effect of alcohol consumption on insulin sensitivity: A systematic review and meta-analysis

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Number of appendices	3
Date	08-03-2013

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SUMMARY

Rationale: Moderate alcohol consumption, compared to non-drinking and heavy drinking, is a life style factor that is consistently related with a reduced risk of DM II. This could be explained by improved insulin sensitivity or glycemic status, but results of intervention studies on this relation are inconsistent.

Aim: To investigate the effect of alcohol consumption on insulin sensitivity and glycemic status.

Design: Systematic review and meta-analysis

Data sources: PubMed and Embase will be searched until May 2013 using a pre-specified search string.

Study selection: Intervention studies on the effect of more than 2 weeks alcohol consumption on biological markers of insulin sensitivity or glycemic status.

Outcome parameters: Insulin sensitivity, insulin, glucose, HbA_{1c}

Data analysis:
- Pooled standardized mean differences (fixed or random effects models).
- Heterogeneity
- Publication bias
- Meta-regression on the influence of type of beverage, dosage and duration.

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INTRODUCTION

In 2012, 371 million people suffered from Diabetes Mellitus (DM) worldwide (IDF). In the Netherlands, Diabetes is the most common chronic disease, with approximately one million people having the disorder in 2011. The expectation exists that this amount will be doubled by the end of 2025. As a consequence of this disease, 40-55% of the people with DM experienced one or more chronic complications and every day about 8 people die because of it (Diabetes Fonds 2013). The health care costs related to DM were approximately 1 billion euro in 2007, which accounted for almost 1.5% of all health care costs in the Netherlands that year (Nationaal Kompas Volksgezondheid 2012). Of the one million people with Diabetes in the Netherlands, 9 out of 10 were diagnosed with type 2 Diabetes (DMII) (Diabetes Fonds 2013). Because of this, the prevention of DM II is of great importance.

These days, there are several factors known that influence the risk of DM II. The most important aspects are life style factors such as overweight/obesity and a low physical activity, but also a family history of DM may be relevant (Mayor 2007). Moderate alcohol consumption, compared to non-drinking and heavy drinking, is a life style factor that is consistently related with a reduced risk of DM II in two meta-analyses (Baliunas et al. 2009; Koppes et al. 2005). This relation between DM II and moderate alcohol consumption could be explained by an increased insulin sensitivity (~7%) or other intermediate markers such as inflammatory factors (~8%) or adiponectin (~25%) (Beulens et al. 2008, 2013). Several intervention studies were done to examine the effect of moderate alcohol consumption on these potential underlying pathways. Recently, a meta-analysis of these interventions was performed to summarize the effects on inflammatory factors and adiponectin. This meta-analysis showed that alcohol consumption significantly increased adiponectin levels but did not affect inflammatory factors (Brien et al. 2011). Unfortunately, for insulin sensitivity only a review and no meta- analysis have been performed to date. This review of Hulthe et al. (2005) showed that evidence from cross-sectional studies suggested a positive association between moderate alcohol consumption and insulin sensitivity, but evidence of the three intervention studies taken into account did not found an effect (Zilkens et al. 2003; Flanagan et al. 2002; Cordain et al. 2000). Several other intervention trials also reported inconsistent results (Davies et al. 2002; Naissides et al. 2006; Napoli et al. 2005; Kim et al. 2009; Sierksma et al. 2004). Consequently, there is no consensus yet about this topic and therefore, a meta- analysis is of great importance.

The underlying mechanism of how alcohol influences insulin sensitivity is also not clearly understood yet, but several suggestions have been made. One of those suggestions is that plasma adiponectin concentrations could be elevated by moderate alcohol consumption, which could be prior to changes in insulin sensitivity (Sierksma et al. 2004). This can be because, according to Yamauchi et al. (2001), adiponectin is able to improve insulin sensitivity by inhibiting glucose production or enhancing glucose uptake and muscle fat oxidation.

Because the review mentioned earlier was mainly based on observational studies and randomized controlled trials are seen as the golden standard for causal relationships, this research will only focus on RCT's. Therefore, the aim of this research is to conduct a systematic review and meta-analysis of randomized controlled trials investigating the effect of alcohol consumption on insulin sensitivity in healthy subjects.

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METHODS

Data sources and searches

A literature search will be conducted in PubMed Medline on intervention studies investigating the effect of alcohol consumption on insulin sensitivity. This will be done by using the pre-specified search-string: "((alcohol [Title/Abstract] OR ethanol [Title/Abstract]) AND (intake [Title/Abstract] OR consumption [Title/Abstract])) OR (alcoholic [Title/Abstract] AND (beverage [Title/Abstract] OR beverages [Title/Abstract] OR drink [Title/Abstract] OR drinks [Title/Abstract])) AND (Insulin [Title/Abstract] OR glycemic control [Title/Abstract] OR glycaemic control [Title/Abstract] OR glycemic response [Title/Abstract] OR glycaemic response [Title/Abstract] OR glucose [Title/Abstract] OR glycated haemoglobin [Title/Abstract] OR glycated haemoglobin [Title/Abstract] OR HbA1c [Title/Abstract]) NOT (Animals [Mesh] NOT Humans [Mesh]) ". Furthermore, references and related citations of articles already found will be searched in order to identify other relevant papers.

The search will especially focus on exposure of interest, relevant outcome measures and study designs and will be ended in week 13. In this study, the exposure of interest will be (moderate) alcohol consumption and the primary outcome measure (whole body) insulin sensitivity. Secondary outcome measures that will be taken into account are insulin, glucose and HbA_{1c}. The study design of interest will be randomized controlled trials with an intervention of alcohol consumption and a control group.

The present research will be carried out in accordance with the PRISMA Statement guidelines for the reporting of systematic reviews and meta- analysis of intervention studies. These guidelines consist of a 27- item checklist and a four-phase flow diagram (Appendix 1).

Study selection

Relevant studies will be selected by two researchers during a multi-phase process based on the following inclusion criteria: intervention study on the effect of alcohol on insulin sensitivity or markers of glycemia, intervention period of more than 2 weeks and written in English or Dutch language. Exclusion criteria will be heavy alcohol drinking/drinkers (≥ 60 grams of alcohol for at least one day per week, Nationaal Kompas Volksgezondheid), and a history of alcoholism.

In the first phase, titles of articles will be reviewed by two researchers in order to select papers for the second round. In this next phase, abstracts of studies reporting on the effects of alcohol consumption and insulin sensitivity will be read to determine if an article seems applicable. If so, the full text will be studied by the two researchers in the third phase to determine if the article meets all criteria and is eligible for inclusion. If there is no consensus between the two researchers about the inclusion of a particular article, a third assessor will be consulted in order to determine if the study will be taken into account. The selection and inclusion of the articles will be shown in a flow diagram (Figure 1).

Data extraction and quality assessment

After the selection of relevant studies, important information like sample size, participants' characteristics, in- and exclusion criteria, study design, duration of intervention and outcome measure will be extracted from the included studies on a pre-specified form (Appendix 2). The most important characteristics will be shown in a table (Table 1). When available, also detailed information about the intervention (e.g. grams alcohol p/d) will be taken into account. If a study did not report the grams of alcohol per unit, 10 g of alcohol per drink will be used for analysis (Turner 1990; Lemmens 1994).

Furthermore, several aspects will be reported regarding the quality of a research, like randomization procedures, compliance to the intervention, drop-out rates and follow up duration (Appendix 3). Additionally, the effects of different types of alcoholic beverages and the dosage given will be taken into account. Blinding of participants to the intervention alcohol intake is not sure to be effective, so will therefore not be assessed in this review.

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Data synthesis and analysis

Besides the quality assessment, also heterogeneity will be investigated. This will be done through calculation of the Q and I^2 statistics, which will be used to determine if a fixed or random effects model for pooling is most appropriate. Is there is significant heterogeneity, a random effects model will be used. Otherwise a fixed model will be most appropriate. Potential publication bias will be examined by the use of a funnel plot and Egger and Begg's statistical tests.

The mean effects of the different studies will be pooled in a meta- analysis and shown in a forest plot. The mean effects on any of the prespecified outcomes (insulin sensitivity, insulin, glucose, HbA_{1c}) will be calculated through (mean effect intervention group) – (mean effect control group) and the meta-analysis will be conducted using the DerSimonian and Laird effects model with the STATA meta-procedure (StataCorp LP, College Station, TX, USA). Because insulin sensitivity is measured using different methods, outcomes may need to be standardized. The Cohen's *d* will be used to calculate the primary effect size, as it enables us to combine results from different measurements. In this way, all effect sizes can be pooled together. The Cohen's *d* will be calculated by the mean difference in insulin sensitivity between the intervention group and control group, divided by the pooled standard deviation. If sufficient studies used the same method for measuring insulin sensitivity, the crude results will be meta-analysed as well. For insulin, glucose and HbA_{1c}, standardisation will not be applicable. In a meta-regression the influence of alcoholic beverage, dosage and duration of intervention on our results will be investigated. All analysis will be done using STATA 10.0.

SUPPLEMENTARY DATA

REFERENCES

Baan CA. (2012) Diabetes mellitus samengevat. *Nationaal Kompas Volksgezondheid*. Bilthoven: RIVM. Report number: 4.10.

Baliunas DO, Taylor BJ, Irving H, Roerecke M, Patra J, Mohapatra S et al. (2009) Alcohol as a risk factor for type 2 diabetes: A systematic review and meta-analysis. *Diabetes Care* 32:2123–32.

Beulens JWJ, Rimm EB, Hu FB, Hendriks HFJ, Mukamal KJ. (2008) Alcohol Consumption, Mediating Biomarkers, and Risk of Type 2 Diabetes Among Middle-Aged Women. *Diabetes Care* 31:2050–2055.

Beulens JWJ, van der Schouw YT, Moons KGM, Boshuizen HC, van der A DL, Groenwold RHH. (2013) Estimating the mediating effect of different biomarkers on the relation of alcohol consumption with the risk of type 2 diabetes. *Annals of Epidemiology* 1047–2797.

Brien SE, Ronksley PE, Turner BJ, Mukamal KJ, Ghali WA. (2011) Effect of alcohol consumption on biological markers associated with risk of coronary heart disease: systematic review and meta-analysis of interventional studies. *BMJ* 342:d636.

Cordain L, Melby CL, Hamamoto AE, O'Neill DS, Cornier M, Barakat H et al. (2000) Influence of moderate chronic wine consumption on insulin sensitivity and other correlates of syndrome X in moderately obese women. *Metabolism* 49:1473–1478.

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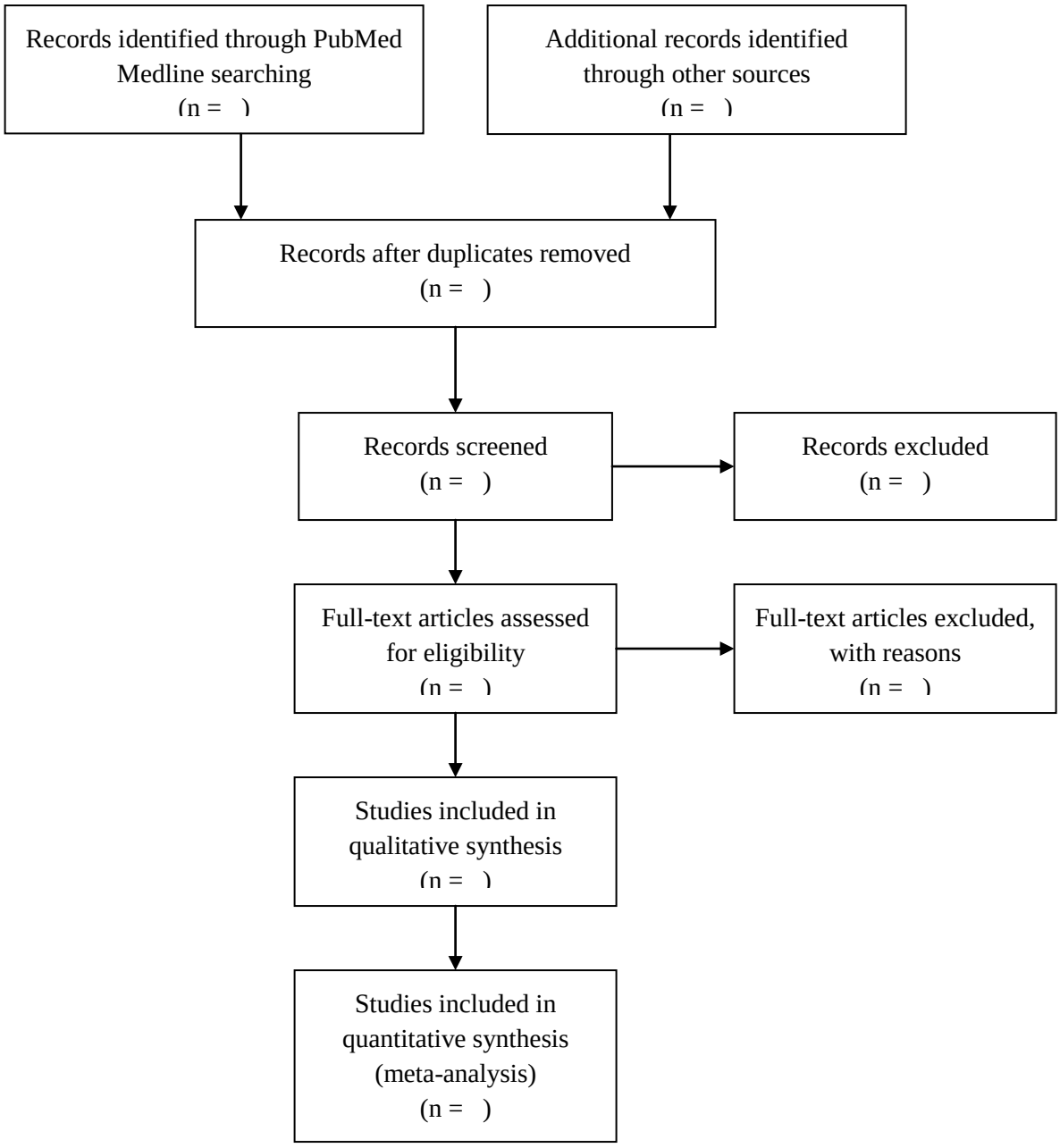
SUPPLEMENTARY DATA

Figure 1. Flow diagram literature search



SUPPLEMENTARY DATA

Table 1. Characteristics of the included studies

Study reference	Design	Participants	Characteristic participants (mean ± sd)	Intervention	Alcohol dosage	Outcome measure	Duration of intervention

SUPPLEMENTARY DATA

LIST OF APPENDICES

Appendix 1. Checklist and Flow diagram PRISMA
Appendix 2. Information form articles
Appendix 3. Quality assessment included studies

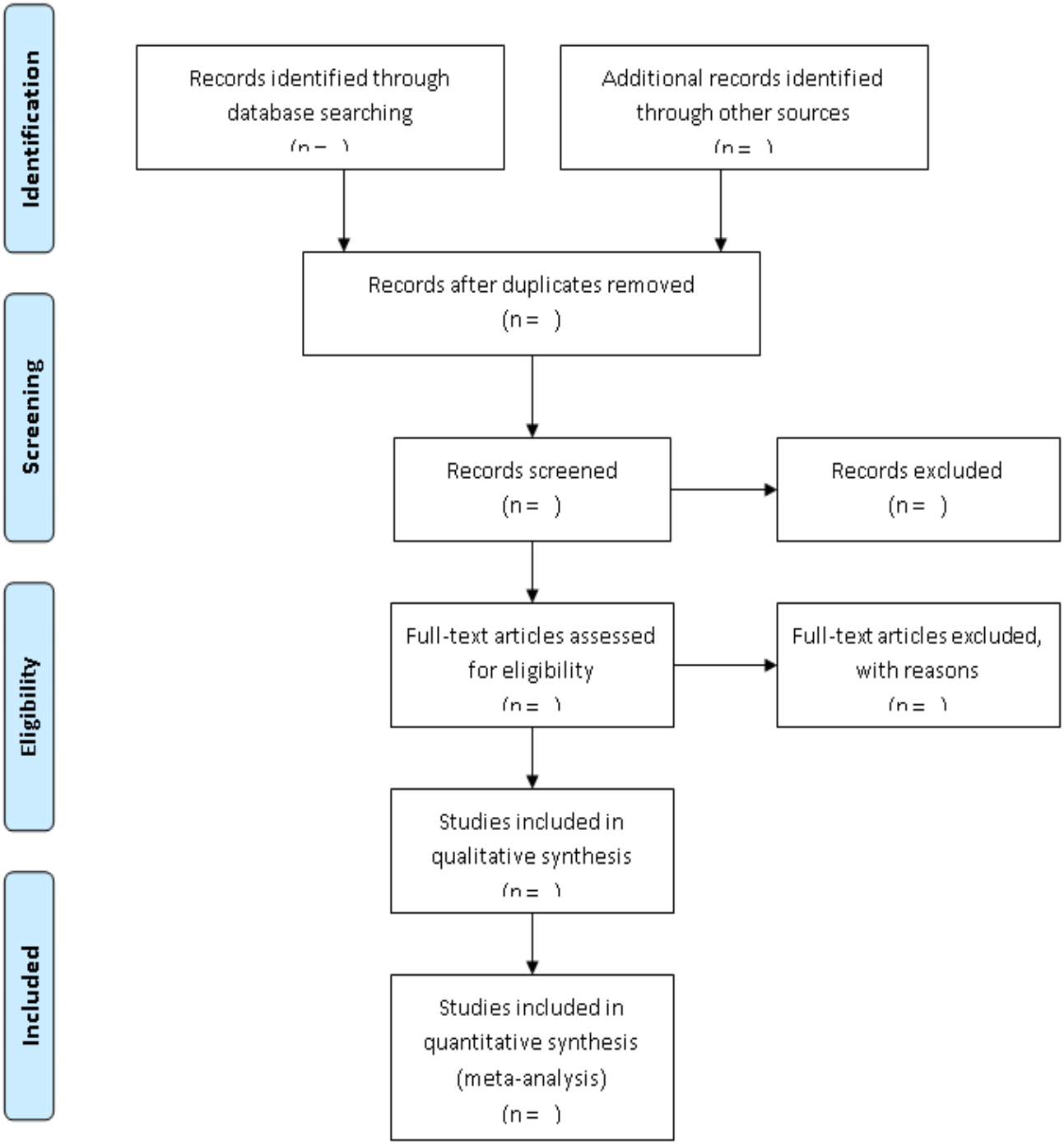
SUPPLEMENTARY DATA

Appendix 1. Checklist and Flow diagram PRISMA

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

SUPPLEMENTARY DATA



SUPPLEMENTARY DATA

Appendix 2. Information form articles

Item	Definition
Journal	
Year	
Volume	
Pages	
Authors	
Study population	
Type of study population	
Number of people in study population	
Inclusion criteria	
Exclusion criteria	
Intervention	
Type of study design	
Method of randomization	
Duration of intervention	
Type of alcoholic beverage	
Alcohol dosage	
Statistics	
Statistical method	
Reported outcome measure(s)	
How is the outcome assessed	
Level of significance	
Result ± SEM/SD intervention group	
Result ±SEM/SD control group	
Funding	
Company	

SUPPLEMENTARY DATA

Appendix 3. Quality assessment included studies

Source	Study design	Randomized	Randomization described	Blinding researcher(s)	Measurement compliance	Follow up duration	Drop out rates	Intention to treat analysis